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Active screening and surveillance in the United Kingdom for Middle East respiratory syndrome coronavirus in returning travellers and pilgrims from the Middle East: a prospective descriptive study for the period 2013–2015

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SUMMARY

Background: Over 25 000 pilgrims from the UK visit Saudi Arabia every year for the Umrah and Hajj pilgrimages. The recent outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) in South Korea and the continuing reports of MERS-CoV cases from Saudi Arabia highlight the need for active surveillance for MERS-CoV in returning pilgrims or travellers from the Middle East. Public Health England Birmingham Laboratory (PHEBL) is one of a few selected UK public health laboratories responsible for MERS-CoV screening in travellers returning to the UK from the Middle East who present to hospital with severe respiratory symptoms. The results of the PHEBL MERS-CoV screening and surveillance over the past 3 years is presented.

Methods: UK travellers/pilgrims who returned from the Middle East and presented to a hospital with respiratory symptoms were studied over the period February 1, 2013 to December 31, 2015. Patients with respiratory symptoms, who satisfied the Public Health England MERS-CoV case algorithm, were tested for MERS-CoV and other respiratory tract viruses on admission to hospital.

Results: Two hundred and two patients suspected of having MERS-CoV were tested. None of them had a laboratory-confirmed MERS-CoV infection. A viral aetiology was detected in half (50.3%) of the cases, with rhinoviruses, influenza A (H1N1 and H3N2), and influenza B being most frequent. Peak testing occurred following the annual Hajj season and in other periods of raised national awareness.

Conclusions: Respiratory tract infections in travellers/pilgrims returning to the UK from the Middle East are mainly due to rhinoviruses, influenza A, and influenza B. Whilst MERS-CoV was not detected in the 202 patients studied, heightened awareness of the possibility of MERS-CoV and continuous proactive surveillance are essential to rapidly identify cases of MERS-CoV and other seasonal respiratory tract viruses such as avian influenza, in patients presenting to hospital. Early identification and isolation may prevent outbreaks in nosocomial settings.

1. Introduction

The Middle East respiratory syndrome coronavirus (MERS-CoV) was first isolated in a patient with fatal pneumonia and renal failure in the Kingdom of Saudi Arabia (KSA) in June 2012.[1] A further nine patients in Jordan were detected retrospectively.[2] The disease was named Middle East respiratory syndrome (MERS) and it presents as a clinical spectrum ranging from asymptomatic to a severe fulminant multisystem disease affecting all organs.[3] MERS-CoV has remained on the radar of global public health authorities since its first discovery in 2012 because of recurrent nosocomial and community outbreaks and its association with severe disease

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and high mortality rates, especially in patients with co-morbidities. MERS-CoV is endemic throughout the Arabian Peninsula,[4] although Saudi Arabia appears to bear the majority of reported cases. MERS-CoV cases have been reported in travellers to the Middle East returning to Europe, North Africa, North America, and Asia.[3,5–7] Whilst primary transmission of MERS-CoV appears to be from camels, evidence of person-to-person and nosocomial transmission of MERS-CoV is well documented.[8,9]

The largest outbreak of MERS-CoV outside the Middle East occurred in South Korea in 2015 and was attributed to poor hospital infection control measures.[9] This outbreak only serves to highlight the continued threat of this novel virus to global health security and calls for all health systems to have proactive MERS-CoV surveillance and screening systems in place for ill returning travellers from the Middle East.

Three of the four laboratory-confirmed cases of MERS-CoV reported in the UK in 2013 were initially identified by the Public Health England Birmingham Laboratory (PHEBL).[8] The first of these cases was in a traveller returning from KSA following a religious pilgrimage. The UK is home to over two million Muslims, who make up 4.8% of the overall population of England and Wales,[10] and these Muslims will visit Mecca and Medina in the KSA for religious purposes at least once in a lifetime. There are three main religious ceremonies or events that occur in KSA,[11] for which over 25 000 pilgrims from the UK travel to KSA each year: (1) the Hajj, which is the main obligatory pilgrimage and attracts up to three million pilgrims per year, (2) Umrah, which is a mini pilgrimage and is undertaken at any time during the year, and (3) Ramadan, the month of fasting. During these events, mass gatherings of pilgrims group together and simultaneously carry out the various religious rituals over a period of days or weeks. These mass gatherings are known to be associated with the transmission of a range of infectious diseases, with respiratory tract infections being exceedingly common.[11]

Birmingham is the second largest city in the UK, and 21% of its population are Muslims.[10] The city also acts as a hub for travel to and from the Middle East from the surrounding areas. The regional public health laboratory situated in Birmingham provides a 7-day service. It is one of the few laboratories in the UK that has been responsible for enhanced surveillance covering the South West, the Midlands and the North of England, for returning travellers with severe respiratory symptoms that fit the clinical and epidemiological criteria of the Public Health England (PHE) MERS-CoV algorithm.[12] A detailed analysis of the results from this continued surveillance for MERS-CoV and other viral respiratory tract infections was conducted, which included the period over the three Hajj seasons of 2013, 2014, and 2015.

2. Materials and methods

2.1. Patients

From February 1, 2013 to December 31, 2015, returning travellers presenting to hospitals in the Midlands, South West, and North England with respiratory symptoms were actively investigated. Risk assessments were performed routinely by liaison between the PHE Birmingham consultant virologist and the referring hospital microbiologist, including advice on infection control precautions for healthcare workers, sample preparation, and transport arrangements. Patients were admitted or moved to hospital side rooms and staff instructed to use FFP3 masks and personal protective equipment (PPE) until MERS-CoV had been excluded by laboratory testing. Local health protection teams were routinely involved, both at the time of presentation and when the results of testing became available.

2.2. Samples

Both upper respiratory tract (URT) samples, such as nose and throat swabs and nasopharyngeal aspirates, and lower respiratory tract (LRT) samples, such as sputum and bronchoalveolar lavage samples, were tested. The sample type provided was dependent on the severity of infection and urgency of testing. PHE ensured that all samples were transported using category B shipping regulations, in accordance with World Health Organization guidance on the regulation for the transport of infectious agents 2013–14,[13] using a specialized courier with a 'same day' delivery service. Microbiology investigations were performed routinely in the local laboratories using PHE guidance on the handling and processing of samples suspected of MERS-CoV.[14] Clotted blood was also requested and serum stored for possible future serological testing.

2.3. Respiratory virus screening

Investigation for MERS-CoV RNA was included in the routine panel of respiratory viruses tested for by qualitative real-time reverse transcription PCR (rRT-PCR), as described elsewhere.[15] The routine panel included testing for influenza A (both H1 and H3), influenza B, respiratory syncytial virus (RSV), rhinoviruses, parainfluenza virus types 1–4, human metapneumovirus, and adenoviruses.

2.4. Statistical methods

The comparison between the likelihood of virus detection and the destination of travel (KSA vs. Dubai) was performed using *Z*-ratio proportion analysis. The comparison of the duration of symptoms with the detection of a viral agent was performed using the Mann–Whitney *U*-test.

3. Results

3.1. Patients

Two hundred and fourteen patients fulfilled the criteria of the PHE case definition algorithm and were tested for MERS-CoV infection. Twelve patients were tested elsewhere due to a 5-month cessation of testing at Birmingham as a result of a PHE policy change; these patients were excluded from the analysis. The remaining 202 patient samples were tested at Birmingham. Patient demographic characteristics are shown in Table 1. The median age of the patients was 54 years (range 4 months to 85 years).

3.2. Sample types

All (100%) of the 202 samples were tested for MERS-CoV and other respiratory viruses and the results were reported within 24 h of sample receipt, which corresponded to the defined PHE turnaround time. Amongst the positive samples, 57% were from the LRT. Since one of the criteria for MERS-CoV testing is evidence of LRT involvement, 39 patients had a sample taken from the LRT in addition to the URT. In this subset, 21 (53.8%) had a virus detected

Table 1
Demographic characteristics of 202 patients tested, February 2013 to December 2015

	0–16 years	17–65 years	>65 years	Total (%)
Male	5	84	28	117 (57.9)
Female	5	55	25	85 (42.1)
Total (%)	10 (5.0)	139 (68.8)	53 (26.2)	202 (100)

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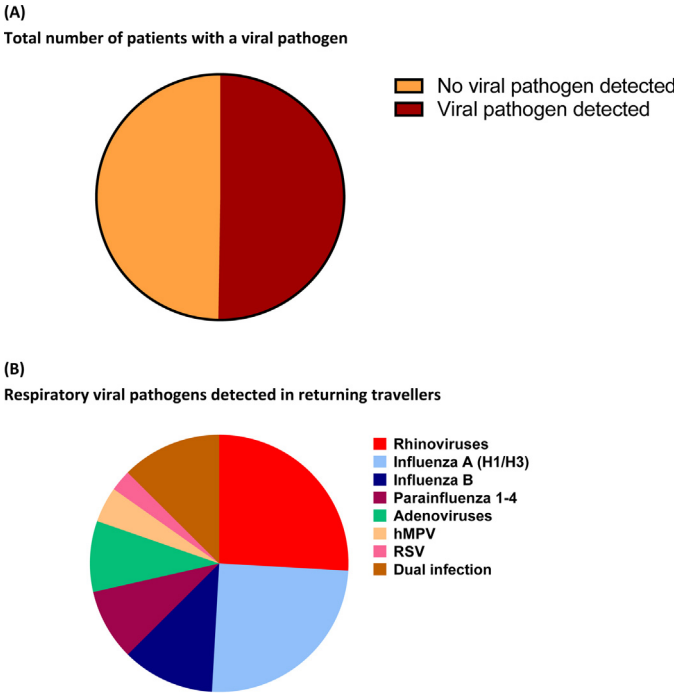

Figure 1. (A) Total number of patients with a viral pathogen. (B) Respiratory viral pathogens detected in returning travellers.

in both samples, 13 (33.4%) had virus detected in the LRT sample only, and five (12.8%) had a virus detected only in the URT sample.

3.3. Respiratory virus detection

Of all the samples obtained from the 202 patients tested, none was MERS-CoV-positive. However, a viral aetiology for clinical illness was found in 50.3% of cases, as shown in Figure 1A.

Figure 1B represents the proportions of all the respiratory viruses detected. An almost equal number of patients were found to be positive for influenza A ($n = 28$; either H1N1 or H3N2) and rhinovirus ($n = 29$). Thirteen (6.4%) of the patients were influenza B-positive and there were 10 cases (5.0%) of parainfluenza virus (types 1–4), 10 (5.0%) of adenovirus, five (2.5%) of RSV, and three (1.5%) of human metapneumovirus. Viral nucleic acid from more than one virus was simultaneously detected in 14 cases (6.7%), with one patient having three viruses detected.

A bacterial diagnosis was reported in seven patients: four were positive for *Legionella pneumophila* and one was positive for *Streptococcus pneumoniae* by urinary antigen testing, one was positive for *Escherichia coli* and one for *Brucella* species on positive blood culture.

3.4. Travel history

Amongst those with a detailed travel history, the main countries visited were KSA (46.2%) and Dubai (35.5%). A small number of travellers were also tested following return from UAE, Oman, and Iraq. A significant difference in proportion of virus detection in patients returning from KSA vs. Dubai was observed ($p < 0.024$).

3.5. Duration of symptoms

The median duration of symptoms prior to sample testing was 5 days (range 1–22 days). No significant difference in symptom duration was observed between patients with or without a positive viral agent detected ($p = 0.384$).

3.6. Peak testing times

During 2013, the greatest number of samples were tested following the first positive MERS-CoV patients identified in Birmingham, rather than during the Ramadan (July–August) or Hajj (November) seasons (Figure 2A).

During 2014, the largest number of samples tested was seen post-Hajj in October (Figure 2B). Similarly, in 2015, the largest number of samples tested was during the post-Hajj season in October (Figure 2C), with an increase in testing also observed following the outbreak reported in South Korea in May 2015.

4. Discussion

During the 3-year period of MERS-CoV surveillance, there were no cases of MERS-CoV detected by laboratory testing in 202 returning pilgrims or other travellers to the UK who presented to hospitals with respiratory symptoms. This concurs with the wider global finding of no record of person-to-person transmission of MERS-CoV during the mass gatherings at the Hajj during the period 2013–15.[16] Since the diagnostic yield of MERS-CoV is dependent on the quality and type of respiratory tract sample,[17] MERS-CoV cases may have been missed. Furthermore, since MERS-CoV causes a wide clinical spectrum of presentations from mild to severe,[3] there is a possibility that returning pilgrims with MERS-CoV infection are being missed since they may recover without presenting to healthcare or may recover before a diagnosis is made. Thus the follow-up of patients to test for seroconversion and further epidemiological studies using serological tests[18] are necessary to establish whether any MERS CoV infections occur in pilgrims that we are unaware of.

The main finding of this study was that approximately 50% of the patient samples had one or more respiratory viruses detected. The viruses most frequently found were influenza A and rhinovirus, in approximately equal proportions. This is in contrast to some previous reports, which have indicated influenza A to be predominant.[19,20] As befits the investigation of a LRT illness, the site of sampling appeared to have a bearing on the likelihood of a virus being detected: almost 60% of all positive results were obtained from LRT samples. Where patients had samples obtained from both the LRT and URT, and thus a direct comparison of results could be made, influenza A was more likely to be detected in LRT samples, whereas rhinovirus, parainfluenza, and influenza B were more likely in URT samples. This finding emphasizes the role played by influenza A in the development of pneumonia, and also the desirability of obtaining the most reliable specimen type to give an accurate diagnosis. This mirrors the optimal approach to the detection of MERS-CoV with the reported pronounced and prolonged shedding of virus from the LRT.[21]

By extension, this frequency of detection of influenza A and B in patients suspected of having MERS-CoV infection also supports the use of empirical antiviral treatment with neuraminidase inhibitors pending the results of laboratory testing. Indeed, the use of antivirals should not be dependent on the prevailing likelihood of circulating influenza in the UK, since most travellers arrived back in the UK outside of the seasonal influenza activity period and most likely had acquired it following exposure to other Hajj pilgrims travelling from the Southern hemisphere.

Analysis of the proportions of travellers being positive for any virus in relation to their travel history showed that a significantly greater proportion were positive if they had travelled from KSA. Since the overwhelming reason for visiting KSA is for religious pilgrimage, this suggests a higher likelihood of viral exposure associated with such a mass gathering. In particular, together with the above data implicating influenza A in the development of LRT infections, it is recommended that a documented history of

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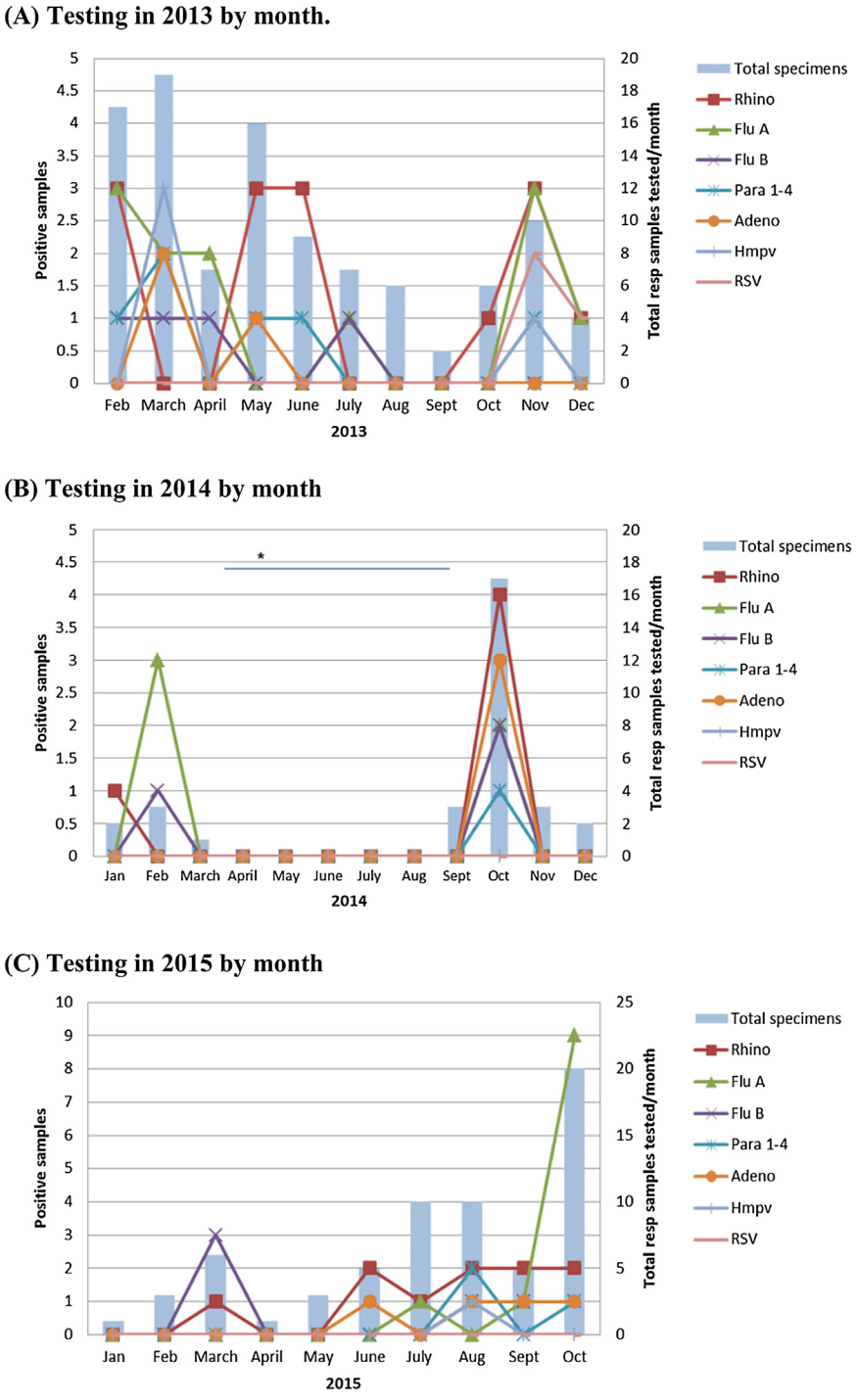

Figure 2. (A) Testing in 2013 by month. (B) Testing in 2014 by month; the asterisk (*) indicates the period of time between April and August 2014 in which testing for MERS-CoV ceased at Public Health England Birmingham Laboratory and testing was transferred to the Public Health England laboratory in London, but resumed post-Ramadan. (C) Testing in 2015 by month.

influenza vaccination within the previous year is introduced as part of the pre-assessment of all Hajj pilgrims, in a similar fashion to the meningococcal vaccine pre-requisite.

All patients had a sample collected for MERS-CoV testing within 24 h of hospital presentation, indicating that the hospital staff showed appropriate awareness of travel risk factors. Peak demand for MERS-CoV testing was associated with times of increased public health awareness of the incidence of MERS; for example, after the detection of three MERS cases in Birmingham, the immediate post-Hajj pilgrimage period, and more recently, during the outbreak in South Korea. Even with these fluctuations in demand, it is imperative to maintain heightened awareness and enhanced surveillance with rapid detection of viral pathogens.[22] This should ensure that an outbreak due to MERS-CoV or other seasonal respiratory viruses, does not result from an undiagnosed returning traveller. MERS-CoV continues to spread within the Middle East and remains a global public health risk. The South Korean outbreak[9] and the nosocomial outbreaks in KSA emphasize the importance of recognizing that healthcare workers can be exposed to MERS-CoV patients seeking medical care.[23,24]

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